Complete Summary

GUIDELINE TITLE

Rheumatoid arthritis. The management of rheumatoid arthritis in adults.

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: the management of rheumatoid arthritis in adults. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Feb. 35 p. (NICE clinical guideline; no. 79).

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Clinical Excellence (NICE). Anakinra for rheumatoid arthritis. London (UK): National Institute for Clinical Excellence (NICE); 2003 Nov. 19 p. (Technology appraisal; no. 72).

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- September 11, 2008 - Rituxan (Rituximab): Genentech informed healthcare professionals of revisions to prescribing information for Rituxan regarding a case of progressive multifocal leukoencephalopathy (PML) leading to death in a patient with rheumatoid arthritis who received Rituxan in a long-term safety extension clinical study.

COMPLETE SUMMARY CONTENT

IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Rheumatoid arthritis (RA)

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Geriatrics
Internal Medicine
Nutrition
Physical Medicine and Rehabilitation
Psychology
Rheumatology
Surgery

INTENDED USERS

Advanced Practice Nurses
Dietitians
Health Care Providers
Health Plans
Nurses
Occupational Therapists
Patients
Pharmacists
Physical Therapists
Physician Assistants
Physicians
Podiatrists
Psychologists/Non-physician Behavioral Health Clinicians

GUIDELINE OBJECTIVE(S)

To provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) in England and Wales that:

- Offers best clinical advice for the management and treatment of rheumatoid arthritis (RA) in adults in primary and secondary care

- Is based on best published clinical and economics evidence, alongside expert consensus
- Takes into account patient choice and informed decision-making
- Defines the major components of NHS care provision for RA
- Details areas of uncertainty or controversy requiring further research
- Provides a choice of guideline versions for different audiences

TARGET POPULATION

Adults with recent onset (disease duration of up to 2 years) and established (disease duration of longer than 2 years) rheumatoid arthritis

Note: This guideline does not cover: patients with other chronic inflammatory polyarthritis.

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Evaluation of presenting symptoms and signs
2. Clinical investigations
    - Rheumatoid factor
    - Anti-cyclic citrullinated peptide
    - X-rays of hands and feet
3. Referral for specialist services

Management/Treatment

1. Communication and education
    - Explanation of risks and benefits of treatment
    - Offering patients participation in self-management programs
    - Verbal and written patient education
2. Use of a multidisciplinary team approach
    - Physiotherapy
    - Occupational therapy
    - Podiatric assessment and review of foot needs
    - Psychological interventions
3. Pharmacological management
    - Disease modifying antirheumatic drugs (DMARDs), including methotrexate
        - Introduction, optimal sequencing, and withdrawal
    - Biological agents*, including rituximab and the tumor necrosis factor alpha inhibitors adalimumab, etanercept, and infliximab
    - When to withdraw DMARDS and biological drugs
    - Glucocorticoids
        - Indications for short-term and long-term use
    - Symptom control
        - Analgesics (paracetamol, codeine, or compound analgesics) to reduce need for long-term treatment with nonsteroidal anti-inflammatory agents (NSAIDS) or cyclo-oxygenase-2 (COX-2) inhibitors
4. Monitoring rheumatoid arthritis
    - C-reactive protein

- Disease activity index (i.e., DAS28)
- Annual review for disease activity, symptom control, functional status, comorbidities, impact of disease on life
- Timing and referral for surgery based on pain, joint function, deformity, and localized synovitis, septic arthritis, cervical myelopathy

5. Other aspects and treatment
    - Diet
    - Complementary therapies

*__Note__: Abatacept was considered but not recommended.

MAJOR OUTCOMES CONSIDERED

- Incidence and prevalence of rheumatoid arthritis
- Clinical effectiveness
- Functional status, symptom relief, quality of life
- Side effects of pharmacologic therapies
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Chronic Conditions (NCC-CC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The information scientist developed a search strategy for each question. Key words for the search were identified by the Guideline Development Group (GDG). In addition, the health economist searched for additional papers providing economics evidence or to inform detailed health economics work (for example, modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified relevant titles and abstracts from the search results for each clinical question and full papers were obtained. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Exclusion criteria used in this guideline were studies that involved a 'non-UK relevant population'. Populations considered to be 'UK-relevant' were Western Europe, North America, Canada, Australia and New Zealand. See Appendix A in the original guideline document for literature search details.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence for Intervention Studies

Level of Evidence	Type of Evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.*
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.*
3	Non-analytic studies (for example case reports, case series).
4	Expert opinion, formal consensus.
*Studies with a level of evidence '–' should not used as a basis for making a recommendation.	

Levels of Evidence for Diagnostic Studies

Level of Evidence	Type of Evidence
Ia	Systematic review (with homogeneity[a]) of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c]

Level of Evidence	Type of Evidence
	Systematic reviews of level-2 studies
III	Level-3 studies[d] Systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

[b] Level-1 studies are studies that use a blind comparison of the test with a validated reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.

[c] Level-2 studies are studies that have only one of the following:

- Narrow population (the sample does not reflect the population to whom the test would apply)
- A poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- A comparison between the test and reference standard that is not blind
- Case-control design.

[d] Level-3 studies are studies that have at least two of the features listed for level-2 studies.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Chronic Conditions (NCC-CC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Appraising the Evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the Guideline Development Group (GDG) for accuracy and completeness. All procedures are fully compliant with:

- NICE methodology as detailed in the Guidelines manual
- NCC-CC quality assurance document and systematic review chart

Health Economics Evidence

Published economics evaluations were retrieved, assessed and reviewed for every guideline question. Full economics evaluations were included – that is those studies that compare the overall health outcomes of different interventions as well as their cost. Cost analyses and cost-consequences analysis, which do not evaluate overall health gain, were not included. Evaluations conducted in the context of non-OECD (Organisation for Economic and Co-operation and Development) countries were also excluded, since costs and care pathways are unlikely to be transferable to the United Kingdom National Health Service. Areas for health economics modelling were agreed by the GDG after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economics modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions, data and structures of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

Distilling and Synthesising the Evidence and Developing Recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations. The criteria for grading evidence are shown in "Rating Scheme for the Strength of the Evidence" below.

Evidence tables are available from the Royal College of Physicians Web site.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Chronic Conditions (NCC-CC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Guideline Development Group (GDG)

The GDG met monthly (June 2007 to July 2008) and comprised (GDG) a multidisciplinary team of health professionals and people with rheumatoid

arthritis, who were supported by the technical team. The GDG membership details, including patient representation and professional groups, are detailed in the GDG membership table at the front of the full version of the original guideline document.

Developing Evidence-Based Questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions, which are shown in Appendix A in the original guideline document.

Agreeing the Recommendations

The GDG employed formal consensus techniques to:

- Ensure that the recommendations reflected the evidence base
- Approve recommendations based on lesser evidence or extrapolations from other situations
- Reach consensus recommendations where the evidence was inadequate
- Debate areas of disagreement and finalise recommendations

The GDG also reached agreement on:

- Recommendations as key priorities for implementation
- Five key research recommendations
- Algorithms

In prioritising key recommendations for implementation, the GDG took into account the following criteria:

- High clinical impact
- High impact on reducing variation in practice
- More efficient use of National Health Service resources
- Allowing the patient to reach critical points in the care pathway more quickly

Writing the Guideline

The first draft version of the guideline was drawn up by the technical team in accordance with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A cost-utility analysis was performed to evaluate the cost-effectiveness of combinations of disease modifying antirheumatic drugs (DMARDs) in the

treatment of patients with recent-onset rheumatoid arthritis. The model also evaluated the cost-effectiveness of using glucocorticoids alongside DMARD monotherapy in patients with recent-onset rheumatoid arthritis. This report detailed the drug combinations investigated, the parameters included within the model, and the structure of the model. The results provided by the model are presented and discussed in Appendix C of the full version of the original guideline document.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline was submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the National Institute for Health and Clinical Excellence (NICE) website, www.nice.org.uk. Editorial responsibility for the full guideline rests with the Guideline Development Group (GDG).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Chronic Conditions (NCC-CC) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The Guideline Development Group (GDG) accepted a clinical diagnosis of Rheumatoid Arthritis (RA) as being more important than the 1987 American Rheumatism Association classification criteria. This is because an early persistent synovitis, in which other pathologies have been ruled out, needs to be treated as if it is RA to try to prevent damage to joints. International committees are addressing the diagnostic criteria for early RA.

The GDG categorised RA into two categories: 'recent onset' (disease duration of up to 2 years) and 'established' (disease duration of longer than 2 years). Within recent-onset RA, categories of suspected persistent synovitis or suspected RA refer to patients in whom a diagnosis is not yet clear, but in whom referral to specialist care or further investigation is required.

Referral, Diagnosis and Investigations

Referral for Specialist Treatment

- Refer for specialist opinion any person with suspected persistent synovitis of undetermined cause. Refer urgently if any of the following apply:
    - The small joints of the hands or feet are affected

    - More than one joint is affected
    - There has been a delay of 3 months or longer between onset of symptoms and seeking medical advice
- Do not avoid referring urgently any person with suspected persistent synovitis of undetermined cause whose blood tests show a normal acute-phase response or negative rheumatoid factor.

Investigations

- Offer to carry out a blood test for rheumatoid factor in people with suspected RA who are found to have synovitis on clinical examination.
- Consider measuring anti-cyclic citrullinated peptide (CCP) antibodies in people with suspected RA if:
    - They are negative for rheumatoid factor
    - There is a need to inform decision-making about starting combination therapy (see section "Introducing and Withdrawing DMARDS" under "Pharmacological Management" below).
- X-ray the hands and feet early in the course of the disease in people with persistent synovitis in these joints.

Communication and Education

- Explain the risks and benefits of treatment options to people with RA in ways that can be easily understood. Throughout the course of their disease, offer them the opportunity to talk about and agree all aspects of their care, and respect the decisions they make.
- Offer verbal and written information to people with RA to:
    - Improve their understanding of the condition and its management
    - Counter any misconceptions they may have
- People with RA who wish to know more about their disease and its management should be offered the opportunity to take part in existing educational activities, including self-management programmes.

The Multidisciplinary Team

- People with RA should have ongoing access to a multidisciplinary team. This should provide the opportunity for periodic assessments (see under "Monitoring Rheumatoid Arthritis" below) of the effect of the disease on their lives (such as pain, fatigue, everyday activities, mobility, ability to work or take part in social or leisure activities, quality of life, mood, impact on sexual relationships) and help to manage the condition.
- People with RA should have access to a named member of the multidisciplinary team (for example, the specialist nurse) who is responsible for coordinating their care.
- People with RA should have access to specialist physiotherapy, with periodic review (see under "Monitoring Rheumatoid Arthritis" below), to:
    - Improve general fitness and encourage regular exercise
    - Learn exercises for enhancing joint flexibility, muscle strength and managing other functional impairments
    - Learn about the short-term pain relief provided by methods such as transcutaneous electrical nerve stimulators [TENS] and wax baths

- People with RA should have access to specialist occupational therapy, with periodic review (see under "Monitoring Rheumatoid Arthritis" below), if they have:
    - Difficulties with any of their everyday activities
    - Problems with hand function
- Offer psychological interventions (for example, relaxation, stress management and cognitive coping skills [such as managing negative thinking]) to help people with RA adjust to living with their condition.
- All people with RA and foot problems should have access to a podiatrist for assessment and periodic review of their foot health needs (see under "Monitoring Rheumatoid Arthritis" below).
- Functional insoles and therapeutic footwear should be available for all people with RA if indicated.

Pharmacological Management

Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

Introducing and Withdrawing DMARDs

- In people with newly diagnosed active RA, offer a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within 3 months of the onset of persistent symptoms.
- Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) to rapidly improve symptoms in people with newly diagnosed RA if they are not already receiving glucocorticoids as part of DMARD combination therapy.
- In people with recent-onset RA receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control.
- In people with newly diagnosed RA for whom combination DMARD therapy is not appropriate (for example, because of comorbidities or pregnancy, during which certain drugs would be contraindicated), start DMARD monotherapy, placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD.
- In people with established RA whose disease is stable, cautiously reduce dosages of disease-modifying or biological drugs. Return promptly to disease-controlling dosages at the first sign of a flare.
- When introducing new drugs to improve disease control into the treatment regimen of a person with established RA, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled.
- In any person with established rheumatoid arthritis in whom disease-modifying or biological drug doses are being decreased or stopped, arrangements should be in place for prompt review.

Glucocorticoids

- Offer short-term treatment with glucocorticoids for managing flares in people with recent-onset or established disease to rapidly decrease inflammation.

- In people with established RA, only continue long-term treatment with glucocorticoids when:
    - The long-term complications of glucocorticoid therapy have been fully discussed
    - All other treatment options (including biological drugs) have been offered

Biological Drugs

- Please see the section below for other NICE technology appraisal guidance on biological drugs for RA.
- On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of RA, except in the context of a controlled, long-term clinical study*.
- Patients currently receiving anakinra for RA may suffer loss of well-being if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop*.

  *__Note__: These recommendations are from 'Anakinra for rheumatoid arthritis', NICE technology appraisal guidance 72. The GDG reviewed the evidence on anakinra but made no changes to the recommendations.

- Do not offer the combination of tumour necrosis factor-alpha (TNF-alpha) inhibitor therapy and anakinra for RA.

Symptom Control

The recommendations under the second through fourth bullets in this section replace the rheumatoid arthritis aspects only of 'Guidance on the use of cyclo-oxygenase (COX) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis' (See the NICE technology appraisal guidance 27).

- Offer analgesics (for example, paracetamol, codeine or compound analgesics) to people with RA whose pain control is not adequate, to potentially reduce their need for long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 (COX-2) inhibitors.
- Oral NSAIDs/COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time.
- When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor (other than etoricoxib 60 mg). In either case, these should be co-prescribed with a proton pump inhibitor (PPI), choosing the one with the lowest acquisition cost.
- All oral NSAIDs/COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, healthcare professionals should take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors.

- If a person with RA needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a PPI) if pain relief is ineffective or insufficient.
- If NSAIDs or COX-2 inhibitors are not providing satisfactory symptom control, review the disease-modifying or biological drug regimen.

Monitoring Rheumatoid Arthritis

- Measure CRP and key components of disease activity (using a composite score such as DAS28) regularly in people with RA to inform decision-making about:
    - Increasing treatment to control disease
    - Cautiously decreasing treatment when disease is controlled
- In people with recent-onset active RA, measure CRP and key components of disease activity (using a composite score such as DAS28) monthly until treatment has controlled the disease to a level previously agreed with the person with RA.
- Offer people with satisfactorily controlled established RA review appointments at a frequency and location suitable to their needs. In addition, make sure they:
    - Have access to additional visits for disease flares
    - Know when and how to get rapid access to specialist care
    - Have ongoing drug monitoring
- Offer people with RA an annual review to:
    - Assess disease activity and damage, and measure functional ability (using, for example, the Health Assessment Questionnaire [HAQ])
    - Check for the development of comorbidities, such as hypertension, ischaemic heart disease, osteoporosis and depression
    - Assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung or eyes
    - Organise appropriate cross referral within the multidisciplinary team
    - Assess the need for referral for surgery (see "Timing and Referral" below)
    - Assess the effect the disease is having on a person's life

Timing and Referral for Surgery

- Offer to refer people with RA for an early specialist surgical opinion if any of the following do not respond to optimal non-surgical management:
    - Persistent pain due to joint damage or other identifiable soft tissue cause
    - Worsening joint function
    - Progressive deformity
    - Persistent localised synovitis
- Offer to refer people with any of the following complications for a specialist surgical opinion before damage or deformity becomes irreversible:
    - Imminent or actual tendon rupture
    - Nerve compression (for example, carpal tunnel syndrome)
    - Stress fracture
- When surgery is offered to people with RA, explain that the main expected benefits are:
    - Pain relief

    - Improvement, or prevention of further deterioration, of joint function
    - Prevention of deformity

Note: Cosmetic improvements should not be the dominant concern.

- Offer urgent combined medical and surgical management to people with RA who have suspected or proven septic arthritis (especially in a prosthetic joint).
- If a person with RA develops any symptoms or signs that suggest cervical myelopathy (for example, paraesthesiae, weakness, unsteadiness, reduced power, extensor plantars)
    - Request an urgent magnetic resonance imaging scan
    - Refer for a specialist surgical opinion
- Do not let concerns about the long-term durability of prosthetic joints influence decisions to offer joint replacements to younger people with RA.

Diet and Complementary Therapies

- Inform people with RA who wish to experiment with their diet that there is no strong evidence that their arthritis will benefit. However, they could be encouraged to follow the principles of a Mediterranean diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on vegetable and plant oils).
- Inform people with RA who wish to try complementary therapies that although some may provide short-term symptomatic benefit, there is little or no evidence for their long-term efficacy.
- If a person with RA decides to try complementary therapies, advise them:
    - These approaches should not replace conventional treatment
    - This should not prejudice the attitudes of members of the multidisciplinary team, or affect the care offered

Related NICE Technology Appraisal Guidance

The recommendations in this section are existing NICE technology appraisal guidance. They were formulated as part of the technology appraisals and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support the recommendations can be found with the individual appraisals.

Rituximab for the Treatment of Rheumatoid Arthritis (NICE Technology Appraisal Guidance 126)

Available at http://guidance.nice.org.uk/TA126

- Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor alpha (TNF-alpha) inhibitor therapy.
- Treatment with rituximab plus methotrexate should be continued only if there is an adequate response following initiation of therapy. An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points

or more. Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 months.
- Treatment with rituximab plus methotrexate should be initiated, supervised and treatment response assessed by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Adalimumab, Etanercept and Infliximab for the Treatment of Rheumatoid Arthritis (NICE Technology Appraisal Guidance 130)

Available at http://guidance.nice.org.uk/TA130

- The TNF-alpha inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics.
    - Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
    - Have undergone trials of two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.
- TNF-alpha inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy.
- Treatment with TNF-alpha inhibitors should be continued only if there is an adequate response at 6 months following initiation of therapy. An adequate response is defined as an improvement in DAS28 of 1.2 points or more.
- After initial response, treatment should be monitored no less frequently than 6-monthly intervals with assessment of DAS28. Treatment should be withdrawn if an adequate response (as defined in the previous recommendation) is not maintained.
- An alternative TNF-alpha inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial 6-month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.
- Escalation of dose of the TNF-alpha inhibitors above their licensed starting dose is not recommended.
- Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules.
- Use of the TNF-alpha inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.
- Initiation of TNF-alpha inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.

Abatacept for the Treatment of Rheumatoid Arthritis (NICE Technology Appraisal Guidance 141)

Available at http://guidance.nice.org.uk/TA141

- Abatacept is not recommended (within its marketing authorisation) for the treatment of people with rheumatoid arthritis.
- Patients currently receiving abatacept for the treatment of rheumatoid arthritis should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

CLINICAL ALGORITHM(S)

An algorithm for diagnosis and treatment of rheumatoid is provided in the full version of the original guideline document.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Use of this guideline will facilitate appropriate management of patients with rheumatoid arthritis (RA), including drug management.

POTENTIAL HARMS

Adverse events associated with pharmacological therapy

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the National Institute for Health and Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

- Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.
- The National Collaborating Centre for Chronic Conditions disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The Healthcare Commission assesses how well National Health Service (NHS) organisations meet core and developmental standards set by the Department of Health in 'Standards for better health' (available from www.dh.gov.uk). Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that NHS organisations should take into account national agreed guidance when planning and delivering care.

NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website ("http://guidance.nice.org.uk/CG79.

- Slides highlighting key messages for local discussion
- Costing tools
    - Costing report to estimate the national savings and costs associated with implementation
    - Costing template to estimate the local costs and savings involved
- Audit support for monitoring local practice

Key Priorities for Implementation

Referral for Specialist Treatment

- Refer for specialist opinion any person with suspected persistent synovitis of undetermined cause. Refer urgently if any of the following apply:
    - The small joints of the hands or feet are affected
    - More than one joint is affected
    - There has been a delay of 3 months or longer between onset of symptoms and seeking medical advice

Disease-Modifying and Biological Drugs

- In people with newly diagnosed active rheumatoid arthritis (RA), offer a combination of disease-modifying anti-rheumatic drugs (DMARDs) (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within 3 months of the onset of persistent symptoms.
- In people with newly diagnosed RA for whom combination DMARD therapy is not appropriate (for example because of comorbidities or pregnancy, during

which certain drugs would be contraindicated), start DMARD monotherapy, placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD.
- In people with recent-onset RA receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control.

Monitoring Disease

- In people with recent-onset active RA, measure C-reactive protein (CRP) and key components of disease activity (using a composite score such as DAS28) monthly until treatment has controlled the disease to a level previously agreed with the person with RA.

The Multidisciplinary Team

- People with RA should have access to a named member of the multidisciplinary team (for example, the specialist nurse) who is responsible for coordinating their care.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Clinical Algorithm
Patient Resources
Quick Reference Guides/Physician Guides
Resources
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: the management of rheumatoid arthritis in adults. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Feb. 35 p. (NICE clinical guideline; no. 79).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Nov (revised 2009 Feb)

GUIDELINE DEVELOPER(S)

National Collaborating Centre for Chronic Conditions - National Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

This guideline offers best practice advice on the care of adults with RA.

Treatment and care should take into account peoples' needs and preferences. People with RA should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If people do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – 'Reference guide to consent for examination or treatment' (2001) (available from www.dh.gov.uk). Healthcare professionals should also follow the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the person's needs. Treatment and care, and the information people are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the person agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Guideline Development Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Group Members: Dr Michael Rudolf, NCC-CC Chair/Respiratory Physician, Ealing Hospital NHS Trust; Dr Chris Deighton, NCC-CC Clinical Advisor/Consultant Rheumatologist, Derby Hospitals NHS Foundation Trust; Mrs Ailsa Bosworth, Patient and Carer Representative, Maidenhead; Dr Jane Hall, Senior Clinical Research Physiotherapist and Hon. Sen. Lecturer, RACE/Physiotherapy Royal National Hospital for Rheumatic Diseases and University of Bath; Dr Alison Hammond, Reader in Rheumatology Rehabilitation, University of Salford; Ms Sheena Hennell, Consultant Nurse, Wirral University Teaching Hospital; Dr Patrick Kiely, Consultant Rheumatologist, St George's NHS Healthcare Trust, London; Dr Raashid Luqmani, Consultant Rheumatologist, Nuffield Orthopaedic Centre and University of Oxford; Dr David Morgan, General Practitioner (non RA specialist), Birmingham; Dr Rachel O' Mahony, NCC-CC Senior Research Fellow; Mrs Enid Quest, Patient and Carer Representative, Bristol; Mrs Isabel Raiman, Community based nurse, Brighton and Hove City Teaching PCT; Mrs Alison Richards, NCC-CC Information Scientist; Professor David L Scott, Consultant Rheumatologist, Kings College Hospital; Ms Jaim Sutton, NCC-CC Project Manager – until March 2008; Mr Jonathan Tosh, ScHARR Health Economist, University of Sheffield; Ms Claire Turner, NCC-CC Senior Project Manager – from April 2008; Dr Louise Warburton, General Practitioner (specialist in RA), Shrewsbury

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

At each Guideline Development Group (GDG) meeting, all GDG members declared any potential conflict of interests. Full declarations are provided in Appendix D of the full version of the original guideline document.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Clinical Excellence (NICE). Anakinra for rheumatoid arthritis. London (UK): National Institute for Clinical Excellence (NICE); 2003 Nov. 19 p. (Technology appraisal; no. 72).

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Rheumatoid arthritis. National clinical guideline for management and treatment in adults. Full guideline. London: Royal College of Physicians; 2009 Feb. 228 p. (Clinical guideline; no. 79). Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

- Rheumatoid arthritis. The management of rheumatoid arthritis in adults. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence; 2009 Feb. 11 p. (Clinical guideline; no. 79). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- Rheumatoid arthritis. The management of rheumatoid arthritis in adults. Audit support. London (UK): National Institute for Health and Clinical Excellence; 2009 10 p. (Clinical guideline; no. 79). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- Rheumatoid arthritis. Costing report. Implementing NICE guidance. London (UK): National Institute for Health and Clinical Excellence; 2009 Feb. 26 p. (Clinical guideline; no. 79). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- Rheumatoid arthritis. Costing template. London (UK): National Institute for Health and Clinical Excellence; 2009. Various p. (Clinical guideline; no. 79). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- Rheumatoid arthritis in adults. Implementing NICE guidance. Slide set. London (UK): National Institute for Health and Clinical Excellence; 2009. 15 p. (Clinical guideline; no. 79). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.
- The guidelines manual 2007. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 April. Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1790. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Rheumatoid arthritis in adults. Understanding NICE guidance - Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence; 2009 Feb. 11 p. (Clinical guideline; no. 79). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1791. 11 Strand, London, WC2N 5HR.

NGC STATUS

This NGC summary was completed by ECRI on March 8, 2006. This NGC summary was updated by ECRI Institute on August 26, 2009.

The National Institute for Health and Clinical Excellence (NICE) has granted the National Guideline Clearinghouse (NGC) permission to include summaries of their Technology Appraisal guidance with the intention of disseminating and facilitating the implementation of that guidance. NICE has not verified this content to confirm that it accurately reflects the original NICE guidance and therefore no guarantees are given by NICE in this regard. All NICE technology appraisal guidance is prepared in relation to the National Health Service in England and Wales. NICE has not been involved in the development or adaptation of NICE guidance for use in any other country. The full versions of all NICE guidance can be found at www.nice.org.uk.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

Readers with questions regarding guideline content are directed to contact the guideline developer.

Copyright/Permission Requests

Date Modified: 10/5/2009